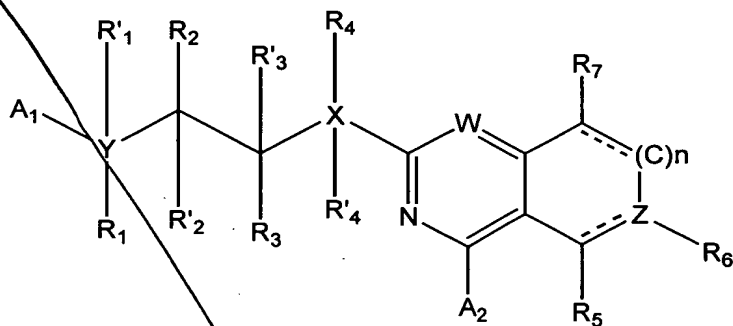


The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

That which is claimed is:

1. A compound having the structure:



wherein:

W and Z are optionally substituted carbon, nitrogen or sulfur;

X and Y are independently selected from the group consisting of nitrogen, oxygen, and optionally substituted carbon;

n is 0, 1 or 2;

A₁ and A₂ are optionally substituted aryl, aryloxy, arylamino or heteroaryl;

R₁, R₂, R₃ and R₄ are independently selected from the group consisting of hydrogen, hydroxyl, and optionally substituted loweralkyl, cycloloweralkyl, alkylaminoalkyl, loweralkoxy, amino, alkylamino, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkylcarbonyl, aryl and heteroaryl;

R'₁, R'₂, R'₃ and R'₄ are independently selected from the group consisting of hydrogen, and optionally substituted loweralkyl;

R₅, R₆ R₇ and are independently selected from the group consisting of hydrogen, hydroxy, halo, carboxyl, nitro, amino, amido, amidino, imido, cyano, and substituted or unsubstituted loweralkyl, loweralkoxy, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkylcarbonyl, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkylaminocarbonyloxy, arylaminocarbonyloxy, formyl, loweralkylcarbonyl, loweralkoxycarbonyl, aminocarbonyl, aminoaryl, alkylsulfonyl, sulfonamido, aminoalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, alkylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, aralkylcarbonylamino, heteroaralkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, amidino, cycloalkyl, cycloamido, cyclothioamido, cycloamidino, heterocycloamidino,

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cycloimido, heterocycloimido, guanidinyl, aryl, biaryl, heteroaryl, heterobiaryl, heterocyclo, heterocycloalkyl, arylsulfonyl and arylsulfonamido; and the pharmaceutically acceptable salts thereof.

~~2. A compound of claim 1 wherein at least one of X and Y is nitrogen.~~

~~3. A compound of claim 2 wherein one of X and Y is nitrogen and the other of X and Y is optionally substituted carbon.~~

~~4. A compound of claim 2 wherein one of X and Y is nitrogen and the other of X and Y is oxygen.~~

~~5. A compound of claim 2, wherein both X and Y are nitrogen.~~

2
6. A compound of claim 1, wherein at least one of A₁ and A₂ is an aromatic ring having from 3 to 10 carbon ring atoms and optionally 1 or more ring heteroatoms.

3
7. A compound of claim 6, wherein at least one of A₁ and A₂ is optionally substituted carbocyclic aryl, arylamino or aryloxy.

4
8. A compound of claim 6, wherein at least one of A₁ and A₂ is optionally substituted heteroaryl.

5
9. A compound of claim 6, wherein at least one of A₁ and A₂ is selected from the group consisting of substituted or unsubstituted phenylamino and phenyloxy.

6
10. A compound of claim 6, wherein at least one of A₁ and A₂ is selected from the group consisting of substituted or unsubstituted pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thiophenyl, furanyl, quinolinyl, purinyl, naphthyl, benzothiazolyl, benzopyridyl, and benzimidazolyl.

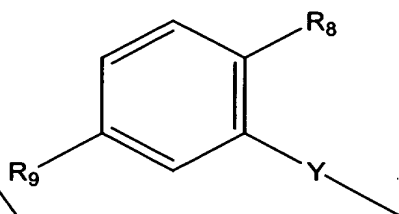
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11. A compound of claim 6, wherein at least one of A₁ and A₂ is substituted with at least one and not more than 3 substitution groups.

8
12.

A compound of claim 11, wherein said substitution groups are independently selected from the group consisting of nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, loweralkyl, haloloweralkyl, loweralkoxy, haloloweralkoxy, loweralkoxyalkyl, loweralkylaminoloweralkoxy, loweralkylcarbonyl, loweraralkylcarbonyl, lowerheteroaralkylcarbonyl, alkylthio, aminoalkyl and cyanoalkyl.

9
13.

A compound of claim 6 wherein at least one of A₁ and A₂ has the formula:



(II)

wherein Y is -NH or -O-; and

R₈ and R₉ are independently selected from the group consisting of hydrogen, nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidiny, sulfonamido, carboxyl, formyl, loweralkyl, haloloweralkyl, loweralkoxy, haloloweralkoxy, loweralkoxyalkyl, loweralkylaminoloweralkoxy, loweralkylcarbonyl, loweraralkylcarbonyl, lowerheteroaralkylcarbonyl, alkylthio, aryl and, aralkyl.

10
14.

A compound of claim 13, wherein A₁ and A₂ are selected from the group consisting of halo and haloloweralkyl.

11
15.

A compound of claim 14, wherein A₁ and A₂ are halo.

12
16.

A compound of claim 13, wherein at least one of A₁ and A₂ is selected from the group consisting of 2,5-dichlorophenylamino and 2,5-dichlorophenyloxy.

13
17.

A compound of claim 1, wherein at least one of R₁, R₂, R₃ and R₄ is substituted loweralkyl selected from the group consisting of hydrogen, unsubstituted or substituted loweralkyl, haloloweralkyl, heterocycloaminoalkyl, and loweralkylaminoloweralkyl.

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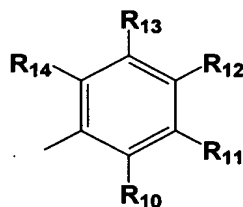
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¹⁴
18. A compound of claim ¹³17, wherein at least one of R₁, R₂, R₃ and R₄ is loweralkylaminoloweralkyl.

¹⁵
19. A compound of claim ¹³17, wherein R₁, R₂, and R₃ are hydrogen and R₄ is selected from the group consisting of hydrogen, methyl, ethyl, aminoethyl, dimethylaminoethyl, pyridylethyl, piperidinyl, pyrrolidinylethyl, piperazinylethyl and morpholinylethyl.

¹⁶
20. A compound of claim 1, wherein at least one of R₅ and R₇ is selected from the group consisting of substituted and unsubstituted aryl, heteroaryl and biaryl.

¹⁷
21. A compound of claim ¹⁶20 wherein at least one of R₅ and R₇ is a substituted or unsubstituted moiety of the formula:



(III)

wherein R₁₀, R₁₁, R₁₂, R₁₃, and R₁₄ are independently selected from the group consisting of hydrogen, nitro, amino, cyano, halo, thioamido, carboxyl, hydroxy, and optionally substituted loweralkyl, loweralkoxy, loweralkoxyalkyl, haloloweralkyl, haloloweralkoxy, aminoalkyl, alkylamino, alkylthio, alkylcarbonylamino, aralkylcarbonylamino, heteroaralkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino aminocarbonyl, loweralkylaminocarbonyl, aminoaralkyl, loweralkylaminoalkyl, aryl, heteroaryl, cycloheteroalkyl, aralkyl, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, arylcarbonyloxyalkyl, alkylcarbonyloxyalkyl, heteroarylcarbonyloxyalkyl, aralkylcarbonyloxyalkyl, and heteroaralkcarbonyloxyalkyl.

¹⁸
22. A compound of claim ¹⁷21 wherein R₁₀, R₁₁, R₁₃, and R₁₄ are hydrogen and R₁₂ is selected from the group consisting of halo, loweralkyl, hydroxy, loweralkoxy, haloloweralkyl, aminocarbonyl, alkylaminocarbonyl and cyano.

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23. A compound of claim 21 wherein R₁₁, R₁₃, and R₁₄ are hydrogen and R₁₀ and R₁₂ are independently selected from the group consisting of halo, loweralkyl, hydroxy, loweralkoxy, haloloweralkyl and cyano.

20
24. A compound of claim 21 wherein R₁₀, R₁₁, R₁₃, and R₁₄ are hydrogen and R₁₂ is heteroaryl.

21
25. A compound of claim 21 wherein R₁₀, R₁₁, R₁₃, and R₁₄ are hydrogen and R₁₂ is a heterocycloalkyl.

22
26. A compound of claim 21 wherein at least one of R₁₀, R₁₁, R₁₂, R₁₃, and R₁₄ are halo and the remainder of R₁₀, R₁₁, R₁₂, R₁₃, and R₁₄ are hydrogen.

23
27. A compound of claim 21 wherein at least one of R₅ and R₇ is selected from the group consisting of dichlorophenyl, difluorophenyl, trifluoromethylphenyl, chlorofluorophenyl, bromochlorophenyl, ethylphenyl, methylchlorophenyl, imidazolylphenyl, cyanophenyl, morphlinophenyl and cyanochlorophenyl.

24
28. A compound of claim 1, wherein R₆ is substituted alkyl selected from the group consisting of aralkyl, hydroxyalkyl, aminoalkyl, aminoaralkyl, carbonylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, aralkylcarbonylaminoalkyl, aminoalkoxyalkyl and arylaminoalkyl.

25
29. A compound of claim 1, wherein R₆ is substituted amino selected from the group consisting of alkylamino, alkylcarbonylamino, alkoxy carbonylamino, arylalkylamino, arylcarbonylamino, alkylthiocarbonylamino, arylsulfonylamino, heteroaryl amino alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, aralkylcarbonylamino, and heteroaralkylcarbonylamino.

26
30. A compound of claim 1, wherein R₆ is selected from the group consisting of unsubstituted or substituted aminocarbonyl, alkyloxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl and alkylaminoalkyloxycarbonyl.

27
31. A compound of claim 1, wherein R₆ is selected from the group consisting of amidino, guanidino, cycloimido, heterocycloimido, cycloamido, heterocycloamido, cyclothioamido and heterocycloloweralkyl.

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32.

29

33.

A compound of claim 1, wherein R₆ is aryl.

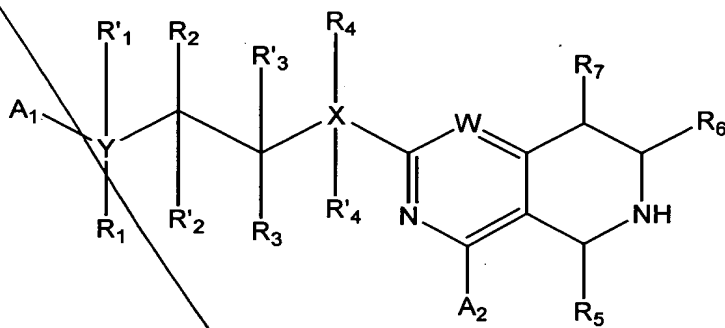
A compound of claim 1, wherein R₆ is heteroaryl.

34. 30

A compound of claim ²⁹33, wherein R₆ is selected from the group consisting of substituted or unsubstituted pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thienyl, furanyl, quinolinyl, pyrrolylpyridyl, benzothiazolyl, benzopyridyl, benzotriazolyl, and benzimidazolyl.

35.

A compound having the structure:



wherein:

W is optionally substituted carbon, nitrogen or sulfur;

X and Y are independently selected from the group consisting of nitrogen, oxygen, and optionally substituted carbon;

A₁ and A₂ are optionally substituted aryl, aryloxy, arylamino or heteroaryl;

R₁, R₂, R₃ and R₄ are independently selected from the group consisting of hydrogen, hydroxyl, and optionally substituted loweralkyl, cycloloweralkyl, alkylaminoalkyl, loweralkoxy, amino, alkylamino, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkylcarbonyl, aryl and heteroaryl;

R'₁, R'₂, R'₃ and R'₄ are independently selected from the group consisting of hydrogen, and optionally substituted loweralkyl;

R₅, R₆ R₇ and are independently selected from the group consisting of hydrogen, hydroxy, halo, carboxyl, nitro, amino, amido, amidino, imido, cyano, and substituted or unsubstituted loweralkyl, loweralkoxy, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteraralkylcarbonyl, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkylaminocarbonyloxy, arylaminocarbonyloxy, formyl, loweralkylcarbonyl, loweralkoxycarbonyl,

aminocarbonyl, aminoaryl, alkylsulfonyl, sulfonamido, aminoalkoxy, alkylamino, arylamino, aralkylamino, heteroaryl, heteroaralkylamino, alkylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, aralkylcarbonylamino, heteroaralkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, amidino, cycloalkyl, cycloamido, cyclothioamido, cycloamidino, heterocycloamidino, cycloimido, heterocycloimido, guanidinyl, aryl, biaryl, heteroaryl, heterobiaryl, heterocyclo, heterocycloalkyl, arylsulfonyl and arylsulfonamido; and the pharmaceutically acceptable salts thereof.

~~36. A compound of claim 35 wherein at least one of X and Y is nitrogen.~~

~~37. A compound of claim 36 wherein one of X and Y is nitrogen and the other of X and Y is optionally substituted carbon.~~

~~38. A compound of claim 36 wherein one of X and Y is nitrogen and the other of X and Y is oxygen.~~

~~39. A compound of claim 36 wherein both X and Y are nitrogen.~~

³²
~~40.~~ ³¹ A compound of claim ~~38~~, wherein at least one of A₁ and A₂ is an aromatic ring having from 3 to 10 carbon ring atoms and optionally 1 or more ring heteroatoms.

³³
~~41.~~ ³² A compound of claim ~~40~~, wherein at least one of A₁ and A₂ is optionally substituted carbocyclic aryl, arylamino or aryloxy.

³⁴
~~42.~~ ³² A compound of claim ~~40~~, wherein at least one of A₁ and A₂ is optionally substituted heteroaryl.

³⁵
~~43.~~ ³² A compound of claim ~~40~~, wherein at least one of A₁ and A₂ is selected from the group consisting of substituted or unsubstituted phenylamino and phenyloxy.

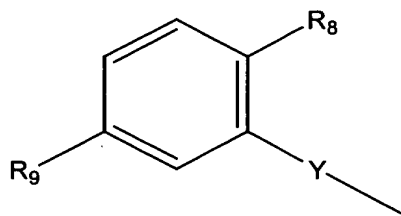
³⁶
~~44.~~ ³² A compound of claim ~~40~~, wherein at least one of A₁ and A₂ is selected from the group consisting of substituted or unsubstituted pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl,

triazolyl, thiophenyl, furanyl, quinolinyl, purinyl, naphthyl, benzothiazolyl, benzopyridyl, and benzimidazolyl.

³⁷
45. A compound of claim ³²40, wherein at least one of A₁ and A₂ is substituted with at least one and not more than 3 substitution groups.

³⁸
46. A compound of claim ³⁷45, wherein said substitution groups are independently selected from the group consisting of nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, loweralkyl, haloloweralkyl, loweralkoxy, haloloweralkoxy, loweralkoxyalkyl, loweralkylaminoloweralkoxy, loweralkylcarbonyl, loweraralkylcarbonyl, lowerheteroaralkylcarbonyl, alkylthio, aminoalkyl and cyanoalkyl.

³⁹
47. A compound of claim ³²40 wherein at least one of A₁ and A₂ has the formula:



(II)

wherein Y is -NH or -O-; and

R₈ and R₉ are independently selected from the group consisting of hydrogen, nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidinyl, sulfonamido, carboxyl, formyl, loweralkyl, haloloweralkyl, loweralkoxy, haloloweralkoxy, loweralkoxyalkyl, loweralkylaminoloweralkoxy, loweralkylcarbonyl, loweraralkylcarbonyl, lowerheteroaralkylcarbonyl, alkylthio, aryl and, aralkyl.

⁴⁰
48. A compound of claim ³⁹47, wherein A₁ and A₂ are selected from the group consisting of halo and haloloweralkyl.

⁴¹
49. A compound of claim ⁴⁰48, wherein A₁ and A₂ are halo.

⁴²
50. A compound of claim ³⁹47, wherein at least one of A₁ and A₂ is selected from the group consisting of 2,5-dichlorophenylamino and 2,5-dichlorophenyloxy.

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51.

A compound of claim 35, wherein at least one of R₁, R₂, R₃ and R₄ is substituted loweralkyl selected from the group consisting of hydrogen, unsubstituted or substituted loweralkyl, haloloweralkyl, heterocycloaminoalkyl, and loweralkylaminoloweralkyl.

44

52.

A compound of claim 51, wherein at least one of R₁, R₂, R₃ and R₄ is loweralkylaminoloweralkyl.

45

53.

A compound of claim 51, wherein R₁, R₂, and R₃ are hydrogen and R₄ is selected from the group consisting of hydrogen, methyl, ethyl, aminoethyl, dimethylaminoethyl, pyridylethyl, piperidiny, pyrrolidinyethyl, piperazinylethyl and morpholinylethyl.

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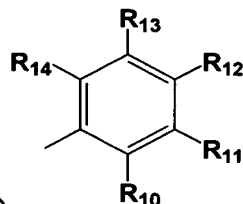
54.

A compound of claim 35, wherein at least one of R₅ and R₇ is selected from the group consisting of substituted and unsubstituted aryl, heteroaryl and biaryl.

47

55.

A compound of claim 54 wherein at least one of R₅ and R₇ is a substituted or unsubstituted moiety of the formula:



(III)

wherein R₁₀, R₁₁, R₁₂, R₁₃, and R₁₄ are independently selected from the group consisting of hydrogen, nitro, amino, cyano, halo, thioamido, carboxyl, hydroxy, and optionally substituted loweralkyl, loweralkoxy, loweralkoxyalkyl, haloloweralkyl, haloloweralkoxy, aminoalkyl, alkylamino, alkylthio, alkylcarbonylamino, aralkylcarbonylamino, heteroaralkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino aminocarbonyl, loweralkylaminocarbonyl, aminoaralkyl, loweralkylaminoalkyl, aryl, heteroaryl, cycloheteroalkyl, aralkyl, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, arylcarbonyloxyalkyl, alkylcarbonyloxyalkyl, heteroarylcarbonyloxyalkyl, aralkylcarbonyloxyalkyl, and heteroaralkylcarbonyloxyalkyl.

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56.

A compound of claim 55 wherein R_{10} , R_{11} , R_{13} , and R_{14} are hydrogen and R_{12} is selected from the group consisting of halo, loweralkyl, hydroxy, loweralkoxy, haloloweralkyl, aminocarbonyl, alkylaminocarbonyl and cyano.

49
57.

A compound of claim 55 wherein R_{11} , R_{13} , and R_{14} are hydrogen and R_{10} and R_{12} are independently selected from the group consisting of halo, loweralkyl, hydroxy, loweralkoxy, haloloweralkyl and cyano.

50
58.

A compound of claim 55 wherein R_{10} , R_{11} , R_{13} , and R_{14} are hydrogen and R_{12} is heteroaryl.

51
59.

A compound of claim 55 wherein R_{10} , R_{11} , R_{13} , and R_{14} are hydrogen and R_{12} is a heterocycloalkyl.

52
60.

A compound of claim 55 wherein at least one of R_{10} , R_{11} , R_{12} , R_{13} , and R_{14} are halo and the remainder of R_{10} , R_{11} , R_{12} , R_{13} , and R_{14} are hydrogen.

53
61.

A compound of claim 55 wherein at least one of R_5 and R_7 is selected from the group consisting of dichlorophenyl, difluorophenyl, trifluoromethylphenyl, chlorofluorophenyl, bromochlorophenyl, ethylphenyl, methylchlorophenyl, imidazolylphenyl, cyanophenyl, morphlinophenyl and cyanochlorophenyl.

54
62.

A compound of claim 31, wherein R_6 is substituted alkyl selected from the group consisting of aralkyl, hydroxyalkyl, aminoalkyl, aminoaralkyl, carbonylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, aralkylcarbonylaminoalkyl, aminoalkoxyalkyl and arylaminoalkyl.

55
63.

A compound of claim 31, wherein R_6 is substituted amino selected from the group consisting of alkylamino, alkylcarbonylamino, alkoxycarbonylamino, arylalkylamino, arylcarbonylamino, alkylthiocarbonylamino, arylsulfonylamino, heteroarylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, aralkylcarbonylamino, and heteroaralkylcarbonylamino.

56
64.

A compound of claim 31, wherein R_6 is selected from the group consisting of unsubstituted or substituted aminocarbonyl, alkyloxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl and alkylaminoalkyloxycarbonyl.

57
65.

A compound of claim ³¹25, wherein R₆ is selected from the group consisting of amidino, guanidino, cycloimido, heterocycloimido, cycloamido, heterocycloamido, cyclothioamido and heterocycloloweralkyl.

58
66.

A compound of claim ³¹35, wherein R₆ is aryl.

59
67.

A compound of claim ³¹35, wherein R₆ is heteroaryl.

60
68.

A compound of claim ⁵⁹61, wherein R₆ is selected from the group consisting of substituted or unsubstituted pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thienyl, furanyl, quinolinyl, pyrrolylpyridyl, benzothiazolyl, benzopyridyl, benzotriazolyl, and benzimidazolyl.

69.

A composition comprising an amount of a compound of claim 1 effective to modulate GSK3 activity in a human or animal subject when administered thereto, together with a pharmaceutically acceptable carrier.

62
70.

A method of inhibiting GSK3 activity in a human or animal subject, comprising administering to the human or animal subject a composition of claim ⁶¹69.

63
71.

A method of treating a cell comprising administering to the cell an amount of a compound of claim 1 effective to inhibit GSK3 activity in the cell.

72.

A method for treating a GSK3-mediated disorder in a human or animal subject, comprising administering to the human or animal subject an amount of a composition of claim 69 effective to inhibit GSK3 activity in the subject.

65
73.

A method of claim ⁶⁴72, wherein the composition is administered by a mode of administration selected from the group consisting of oral, subcutaneous, transdermal, transmucosal, iontophoretic, intravenous, intrathecal, buccal, sublingual, intranasal, and rectal administration.

66
74.

A method of claim ⁶⁴72, wherein said GSK3-mediated disorder is selected from the group consisting of diabetes, ~~Alzheimer's disease~~, obesity, atherosclerotic cardiovascular disease, essential hypertension, polycystic ovary

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syndrome, syndrome X, ischemia, traumatic brain injury, bipolar disorder, immunodeficiency and cancer.

75. A method of claim 74, which further comprises administering to the subject one or more additional active agents.

76. A method of claim 75, wherein the GSK3-mediated disorder is diabetes and the additional active agent is selected from the group consisting of insulin, troglitazone, rosiglitazone, pioglitazone, glipizide and metformin.

77. A compound of claim 1 for use as a pharmaceutical.

78. Use of a compound of claim 1 in the manufacture of a medicament for the treatment of diabetes, Alzheimer's disease and other neurodegenerative disorders, obesity, atherosclerotic cardiovascular disease, essential hypertension, polycystic ovary syndrome, syndrome X, ischemia, traumatic brain injury, bipolar disorder or cancer.

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